Hepatitis Delta: what are the new developments, what are the challenges?

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4th CEE Meeting on Viral Hepatitis and HIV
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I have received consultancy and/or lecture fees from AbbVie, BMS, Gilead, Eiger, Roche, Merck, and have received grants from BMS, Eiger and Roche.
Challenges

New developments
Global overall estimated HDV prevalence: ~5% (4.7-5.3%) of patients with active HBV (240 million HBV cases worldwide--WHO)

HDV is not evenly distributed.
-- low prevalence regions driven primarily by high risk groups
e.g. US (orphan designation 11/25/13), EU, Japan
-- regions of higher prevalence--endemic
e.g. Mongolia, parts of Pakistan, Brasil, Africa, Turkey, etc.
Conclusion  We found that approximately 10.58% HBsAg carriers (without IVDU and HRSB) were coinfected with HDV, which is twofold of what has been estimated before. We also noted a substantially higher HDV prevalence in the IVDU and HRSB population. Our study highlights the need for increased focus on the routine HDV screening and rigorous implementation of HBV vaccine programme.
Findings Of 374 studies identified by our search, 30 were included in our study, only eight of which included detection of hepatitis D virus RNA among anti-hepatitis D virus seropositive participants. In west Africa, the pooled seroprevalence of hepatitis D virus was 7.33% (95% CI 3.55–12.20) in general populations and 9.57% (2.31–20.43) in liver-disease populations. In central Africa, seroprevalence was 25.64% (12.09–42.00) in general populations and 37.77% (12.13–67.54) in liver-disease populations. In east and southern Africa, seroprevalence was 0.05% (0.00–1.78) in general populations. The odds ratio for anti-hepatitis D virus detection among HBsAg-positive patients with liver fibrosis or hepatocellular carcinoma was 5.24 (95% CI 2.74–10.01; p<0.0001) relative to asymptomatic controls.
Prevalence of hepatitis D virus infection in sub-Saharan Africa: a systematic review and meta-analysis

Alexander J Stockdale, Mas Chaponda, Apostolos Beloukas, Richard Odame Phillips, Philippa C Matthews, Athanasios Papadimitropoulos, Simon King, Laura Bonnett, Anna Maria Geretti

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**EEA HDV Prevalence**

Heavily impacted by Immigration and IVDU* Populations

<table>
<thead>
<tr>
<th>Country</th>
<th>High Risk Group Proportion in HDV Population</th>
<th>IVDU HBsAg (+) Population¹</th>
<th>Immigrant HBsAg (+) Population²</th>
<th>High Risk HBsAg (+) Population</th>
<th>% HDV Prevalence³</th>
<th>HDV subjects in High Risk Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>96%</td>
<td>1,686</td>
<td>155,459</td>
<td>157,145</td>
<td>6-9</td>
<td>11,786</td>
</tr>
<tr>
<td>Sweden</td>
<td>84%</td>
<td>4,466</td>
<td>50,593</td>
<td>55,059</td>
<td>2-5</td>
<td>1,927</td>
</tr>
<tr>
<td>France</td>
<td>83%</td>
<td>50,562</td>
<td>112,704</td>
<td>163,266</td>
<td>6-9</td>
<td>12,245</td>
</tr>
<tr>
<td>UK</td>
<td>74%</td>
<td>29,367</td>
<td>192,128</td>
<td>221,495</td>
<td>6-9</td>
<td>16,612</td>
</tr>
<tr>
<td>Germany</td>
<td>72%</td>
<td>9,394</td>
<td>282,256</td>
<td>291,650</td>
<td>10-12</td>
<td>32,082</td>
</tr>
<tr>
<td>Italy</td>
<td>56%</td>
<td>36,940</td>
<td>202,648</td>
<td>239,588</td>
<td>6-9</td>
<td>17,969</td>
</tr>
</tbody>
</table>

¹ IVDU population figures taken from EMCDDA (European Monitoring Center for Drugs and Drug Addiction)
² Immigrant population figures taken from Eurostat
³ HDV prevalence from post-2006 country specific literature reports

- High risk group proportion in HDV population is 56-96%
  - For Spain, Sweden, France, UK, Germany, and Italy, HDV proportion of high risk groups are 96%, 84%, 83%, 74%, 72%, 56%, respectively (mean = 78%).

- Total HDV Population = HDV High Risk Group + HDV Low Risk Group
- HDV High Risk Group = [High risk group HBsAg(+) pop] x [% HDV Prevalence]

  > HBsAg(+) High Risk Group = HBsAg(+) Immigrant Pop + HBsAg(+) IVDU Pop

Changing Hepatitis D Virus Epidemiology in a Hepatitis B Virus Endemic Area With a National Vaccination Program

Hsi-Hsun Lin,1,2 Susan Shin-Jung Lee,3,4 Ming-Lung Yu,5 Ting-Tsung Chang,6,7 Chien-Wei Su,1,3,8 Bor-Shen Hu,9 Yaw-Sen Chen,10 Chun-Kai Huang,5 Chung-Hsu Lai,5 Jiun-Nong Lin,2 and Jaw-Ching Wu1,11

![Graph showing HDV seroprevalence in different groups.](image)
HDV prevalence among HBsAg (+) patients without risk factors

Chen HY et al, Gut 2018 in press
HDV prevalence in the HBsAg (+) IVDU population

Chen HY et al, Gut 2018 in press
Global estimation of HDV in the general population

<table>
<thead>
<tr>
<th>Location</th>
<th>Population/thousands</th>
<th>Prevalence/% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benin</td>
<td>10 576</td>
<td>3.74 (2.44 to 5.29)</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>99 873</td>
<td>0.60 (0.20 to 1.75)</td>
</tr>
<tr>
<td>Gabon</td>
<td>1 930</td>
<td>3.03 (0.51 to 7.43)</td>
</tr>
<tr>
<td>Mauritania</td>
<td>4 182</td>
<td>2.40 (1.76 to 3.13)</td>
</tr>
<tr>
<td>Niger</td>
<td>19 897</td>
<td>5.04 (2.91 to 8.60)</td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>319 929</td>
<td>0.00 (0.00 to 2.89)</td>
</tr>
<tr>
<td>South America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>205 962</td>
<td>2.09 (0.37 to 5.10)</td>
</tr>
<tr>
<td>Colombia</td>
<td>48 229</td>
<td>1.22 (0.72 to 1.84)</td>
</tr>
<tr>
<td>Venezuela</td>
<td>31 155</td>
<td>0.92 (0.28 to 1.86)</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mongolia</td>
<td>2 977</td>
<td>8.03 (5.26 to 12.08)</td>
</tr>
<tr>
<td>China</td>
<td>13 970 293</td>
<td>0.45 (0.15 to 0.89)</td>
</tr>
<tr>
<td>Iran</td>
<td>79 360</td>
<td>0.11 (0.03 to 0.22)</td>
</tr>
<tr>
<td>Japan</td>
<td>127 975</td>
<td>0.73 (0.04 to 2.15)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>189 381</td>
<td>2.43 (1.63 to 3.62)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>31 557</td>
<td>0.39 (0.06 to 0.95)</td>
</tr>
<tr>
<td>Thailand</td>
<td>68 658</td>
<td>0.00 (0.00 to 9.41)</td>
</tr>
<tr>
<td>Turkey</td>
<td>78 271</td>
<td>0.03 (0.01 to 0.08)</td>
</tr>
<tr>
<td>Vietnam</td>
<td>93 572</td>
<td>0.24 (0.07 to 0.87)</td>
</tr>
<tr>
<td>Yemen</td>
<td>26 916</td>
<td>0.14 (0.00 to 0.53)</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albania</td>
<td>2 923</td>
<td>0.45 (0.20 to 0.97)</td>
</tr>
<tr>
<td>France</td>
<td>64 457</td>
<td>0.00 (0.00 to 0.00)</td>
</tr>
<tr>
<td>Greece</td>
<td>11 218</td>
<td>0.00 (0.00 to 1.15)</td>
</tr>
<tr>
<td>Italy</td>
<td>59 504</td>
<td>0.33 (0.27 to 0.39)</td>
</tr>
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</table>

Chen HJ et al, Gut 2018 in press
RESUME

Order anti HDV test in every HBsAg (+) pt.

Even in Sweden, and especially in China

AT THE VERY LEAST: Order anti HDV test if HBsAg (+), ALT high, HBV DNA low even if she/he looks very “NASHy”

ALT high, HBV DNA high, ALT continues to be high despite NA tx
Time free from liver decompensation or death in HIV infected patients

Treatment of CHD

INTERFERON
HCC in CHB vs CHD under treatment

Keskin O et al, AASLD 2016
HDV RNA and HBsAg kinetics under Peg IFN

Long delay before PegIFN affects HDV RNA (median 8.5 days) In HBV, or HCV, effect on HBV DNA or HCV RNA within hours

Guedj et al, Hepatology 2014
Hepatitis D > Hepatitis B

Hepatitis D = Hepatitis B

Hepatitis D < Hepatitis B
HBcAg IHC in CDH

Nuclear localization

No correlation with liver injury, even in HBV-HDV co-dominant cases

Kabaçam et al, Liver Int 2013
HDAG IHC in CDH

HDAG display (+) correlation with ALT and HBsAg levels

Kabaçam et al, Liver Int 2013
VIRAL DOMINANCE PATTERN IN THE HIDIIT-2 STUDY

Lutterkort GL et al, J Viral Hepar 2018
Late response to IFN treatment of D-Dominant HDV

Lutterkort GL et al, J Viral Hepar 2018
IFN treatment of CDH

Interferon without effect in vitro in cell lines supporting HDV replication\(^1,2\)

HDV impairs IFN-stimulated JAK-STAT signalling pathway\(^3\)

Interferon inhibits HDV infection at an early step of infection, at the level of hepatocyte entry\(^4\)

\(^1\)Chang et al, J Virol 2006; \(^2\)Ilan et al, JID 1992; \(^3\)Pugnale et al, Hepatology 2009; \(^4\)Han et al, Plos one 2011
Hepatitis D virus replication is sensed by MDA5 and induces IFN-β/λ responses in hepatocytes

Zhenfeng Zhang¹, Christina Filzmayer¹, Yi Ni¹, Holger Sültmann²,³,⁴, Pascal Mutz¹,⁸, Marie-Sophie Hiet¹, Florian W.R. Vondran⁵,⁶, Ralf Bartenschlager¹,⁷,⁸, Stephan Urban¹,⁷,*
What is the Optimal Dose and Duration of Treatment with pegIFN-α in HDV?

16 MVR (-)  20 MVR (-)  9 MVR (-)  11 MVR (-)  4 MVR (-)  4 MVR (-)
16 MVR (+)  6 MVR (+)  2 MVR (+)  4 MVR (+)  3 MVR (+)  4 MVR (+)

n: 99 -> n: 67 -> n: 41 -> n: 30 -> n: 15 -> n: 8

Yurdaydin et al, JID 2018
What’s Next in HDV Therapy and When?

Entry Inhibitors

Nucleic Acid Polymers

Prenylation Inhibitors
Endpoints in HDV Treatment

• Ideal endpoint: Cure from HDV infection and from HDV disease
  - Cosmic endpoint
• Optimal endpoint: HBsAg (-), HBsAb (+)
  - Back to Earth: very good and very rare
• “Good” endpoints:
  - Post-Tx Week 24 undetectable HDV RNA
  - EOT undetectable HDV RNA
• Acceptable endpoint:
  - EOT ≥ 2 log decline ± normal ALT
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Manuscript under revision
## Characteristics of Novel Drug Treatment for HDV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action</th>
<th>Administration route, Phase of study</th>
<th>Phase of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myrcludex B</td>
<td>Interferes with HDV entry into hepatocyte through NTCP inhibition</td>
<td>Subcutaneous, daily for 6 months, ± Peg-IFN</td>
<td>Ib, II</td>
</tr>
<tr>
<td>Lonafarnib</td>
<td>Farnesyl transferase inhibitor, inhibits virion assembly</td>
<td>Oral, 2 to 12 months, ± ritonavir ± Peg-IFN</td>
<td>II</td>
</tr>
<tr>
<td>Rep-2139-Ca</td>
<td>Nucleic acid polymer, binds with high affinity to amphipathic proteins which are required at various stages of the viral life cycle</td>
<td>Intravenous infusion, once weekly for 4-6 months ± Peg-IFN</td>
<td>II</td>
</tr>
</tbody>
</table>
• 6 of 7 patients experienced HDV RNA decline $>1 \log_{10}$ at week 24 during Myr B monotherapy (mean log decline: $1.67 \log_{10}$ copies/mL)

• 7 of 7 patients experienced HDV RNA decline $>1 \log_{10}$ at week 24 during Myr B/pegIFN-α combination therapy (mean log decline: $2.59 \log_{10}$ copies/mL)

• HDV RNA became negative in 2 patients during MyrB monotherapy and in 5 patients in combination with pegIFN-α

Bogomolov et al, J Hepatol 2016
Myrcludex B Phase 2 Results

Primary endpoint: 2 log HDV RNA decline or negativation week 24

ALT normalization (week 24)

Wedemeyer et al, EASL 2018
Prenylation Inhibitor: Lonafarnib (LNF)

Phase 2 LOWR-1 Study

LOWR HDV = LOnafarnib With Ritonavir in HDV
Yurdaydin et al, Hepatology 2018
Addition of PEG IFN-α Provides Better Activity

Improvement of -2.39 Log IU/mL at Week 24

- LNF 25 mg BID + RTV 100 mg BID + PEG IFN-alfa 180 mcg QW (N=5)
- LNF 25 mg BID + RTV 100 mg BID (N=6)

Change in Log HDV RNA IU / mL

Week

P-value = 0.009

Per protocol analysis

Yurdaydin et al, EASL 2018
Nucleic Acid Polymers (NAPs): Phase 2 Study

Weekly IV Infusions

- 12 Caucasian patients with confirmed chronic HBV / HDV co-infection
  - Clinicaltrials.org # NCT02233075

REP 2139-Ca
500mg qW IV 15 weeks

REP 2139-Ca
250mg qW IV 15 weeks

Pegylated interferon α-2a
180 μg qW SC 48 weeks

Follow-up
(4, 12 and 24 weeks)

REP 301-LTF (NCT02876419): 3 year extension of follow-up (every 6 months)
Nucleic Acid Polymers (NAPs): Phase 2 Results

Weekly IV Infusions

REP 2139-Ca

REP 2139-Ca

HDV RNA negative in 7/12 (58%)
HBsAg negative in 5/12 (42%)
Anti HBs positive at high titers in 5/12 (42%)

Bazinet et al, Lancet Gastroenterol Hepatol 2017
Reported Side Effects of New Drugs for CHD

Myrcludex B:
- Lipase, amylase elevation in phase I but not in phase II study
- Elevation of taurine- and glycine-conjugated bile acids- without apparent clinical consequences
- Thrombocytopenia, neutropenia, lymphopenia and eosinophilia: generally mild, transient

Lonafarnib (LNF):
- Gastrointestinal toxicity: anorexia, nausea ± vomiting, diarrhea, weight loss: dose dependent and in lower dose cohorts generally mild and well tolerated

Nucleic acid polymers (NAPs):
- Hair loss, dysphagia, anorexia, dysgeusia in HBV Study: related to heavy metal exposure at the trial site?
- Administration route related side effects: peripheral grade 1 hyperemia, fever, chills, headache
New Drugs

• Registration studies expected to start soon for Myrcludex B and Lonafarnib
• Nucleic acid polymers: sc formula adaptation and small pilot study to be followed by registration study
• There are others:
  – Small interfering RNAs
  – Immunological approaches: Interferon lambda, TLR agonists, check point inhibitors, HBV vaccines
• Functional cure for HBV
Summary and Conclusion

The only effective treatment is with interferons.

Treatment beyond 1 year needed in a sizeable proportion of patients.

New drugs: promising.

PegIFN-α may still be used as backbone.

We are expecting to enter a new era in the management of CHD.
Summary and Conclusion

Realistic approach suggests a ‘Cascade Approach’

In Africa and may be in China HBV vaccination is key with special emphasis on birth dose
Thank you